CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74252

Trade Name Cimetidine Hydrochloride Injection 150mg/ml

Generic Name Cimetidine Hydrochloride Injection 150mg/ml

Sponsor Gensia Laboratories, Ltd

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74252

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74252

APPROVAL LETTER

ANDA 74-252

NOV 26 1997

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92618

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL.

Reference is also made to your amendments dated March 28, September 10, November 6, and November 24, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tagamet® Injection, 300 mg (base)/2 mL of SmithKline Beecham Pharmaceuticals).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

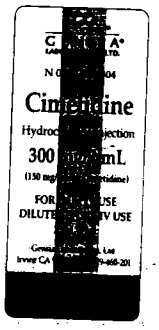
12-26597

CENTER FOR DRUG EVALUATION AND RESEARCH

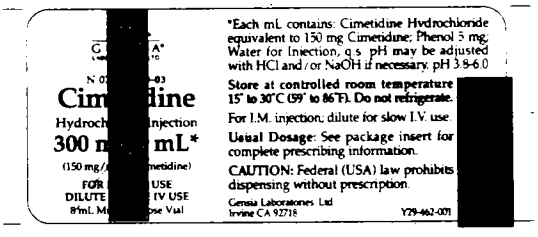
APPLICATION NUMBER 74252

FINAL PRINTED LABELING

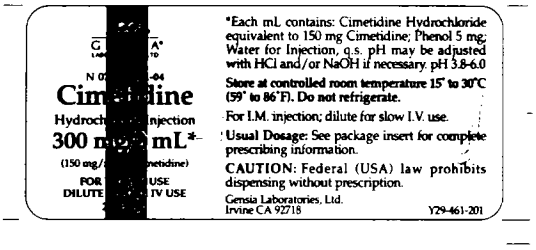
CONTAINER LABEL, NDC # 0703-4602-04
(Part No. Y29-460-201)
300 mg/2 mL
2 mL vial



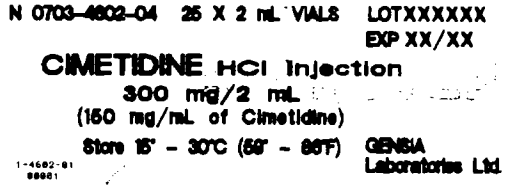
CONTAINER LABEL, NDC # 0703-4620-03
(Part No. Y29-462-001)
300 mg/2 mL
8 mL multiple dose vial



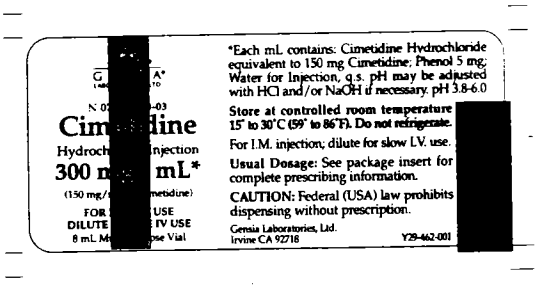
SHELF PACK "A" LABEL NDC # 0703-4602-04
(Part No. Y29-461-201)
300 mg/2 mL
2 mL vial



SHELF PACK "B" LABEL NDC # 0703-4602-04
(Part No. 1-4602-01)
300 mg/2 mL
2 mL vial



SHELF PACK "A" LABEL NDC # 0703-4620-03
(Part No. Y29-462-001)
300 mg/2 mL
8 mL multiple dose vial



SHELF PACK "B" LABEL NDC # 0703-4620-03
(Part No. 1-4620-01)
300 mg/2 mL
8 mL multiple dose vial

N 0703-4620-03 10 x 8 mL VIALS LOT XXXXXX
EXP XX/XX

CIMETIDINE HCl Injection
300 mg/2 mL
(150 mg/mL of Cimetidine)
Store at 15° - 30°C(59° - 86°F)

GENSIA
Laboratories, Ltd.

1-4620-01
00001

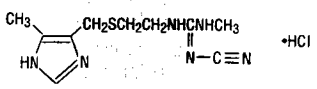
APPROVED

GENSIA®
LABORATORIES, LTD.

Cimetidine
Hydrochloride Injection

DESCRIPTION

Cimetidine is a histamine H_2-receptor antagonist. Chemically it is *N*''-cyano-*N*-methyl-*N*'-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl]-guanidine. The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S$•HCl; and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:



Cimetidine contains an imidazole ring and is chemically related to histamine. (The injection dosage form contains cimetidine hydrochloride.) Cimetidine has a bitter taste and characteristic odor. Cimetidine hydrochloride injection is for I.V. or I.M. administration.

Solubility Characteristics: Cimetidine hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform, and practically insoluble in ether.

Cimetidine Hydrochloride Injection is a sterile aqueous solution. Each mL contains: cimetidine hydrochloride equivalent to 150 mg of cimetidine; phenol 5 mg; water for injection, q.s. pH may be adjusted with HCl and/or NaOH if necessary. pH range is 3.8-6.0.

CLINICAL PHARMACOLOGY

Cimetidine competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2-receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine, and insulin.

Antisecretory Activity

1. Acid Secretion: *Nocturnal:* Cimetidine 800 mg orally at bedtime reduces mean hourly H^+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. Cimetidine 1600 mg orally h.s. produces 100% inhibition of mean hourly H^+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H^+ activity by 35% for an additional five hours into the following morning. Cimetidine 400 mg b.i.d. and 300 mg q.i.d. decrease nocturnal acid secretion in a dose-related manner, i.e., 47% to 83% over a six- to eight-hour period and 54% over a nine-hour, period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours, cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours, and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24-Hour Mean H^+ Activity: Cimetidine 800 mg h.s., 400 mg b.i.d., and 300 mg q.i.d. all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg h.s. regimen exerts its entire effect on nocturnal acid and does not affect daytime gastric physiology.

Chemically Stimulated: Oral cimetidine significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine, and insulin as follows:

Stimulant	Stimulant Dose	Cimetidine	% Inhibition
Betazole	1.5 mg/kg (sc)	300 mg (p.o.)	85% at 2 1/2 hours
Pentagastrin	6 mcg/kg/hr (i.v.)	100 mg/hr (i.v.)	60% at 1 hour
Caffeine	5 mg/kg/hr (i.v.)	300 mg (p.o.)	100% at 1 hour
Insulin	0.03 units/kg/hr (i.v.)	100 mg/hr (i.v.)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45 to 75%, and the inhibition of volume ranged from 30 to 65%.

Parenteral administration also significantly inhibits gastric acid secretion. In a crossover study involving patients with active or healed duodenal or gastric ulcers, either continuous I.V. infusion of cimetidine 37.5 mg/hour (900 mg/day) or intermittent injection of cimetidine 300 mg q6h (1200 mg/day) maintained gastric pH above 4.0 for more than 50% of the time under steady-state conditions.

2. Pepsin: Oral cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

3. Intrinsic Factor: Intrinsic factor secretion was studied with betazole as a stimulant. Oral cimetidine 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying: Cimetidine has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics

The half-life of cimetidine is approximately 2 hours. Both oral and parenteral (I.V. or I.M.) administration provides comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

Steady-state blood concentrations of cimetidine with continuous infusion of cimetidine hydrochloride injection are determined by the infusion rate and clearance of the drug in the individual patient. In a study of peptic ulcer patients with normal renal function, an infusion rate of 37.5 mg/hour produced average steady-state plasma cimetidine concentrations of about 0.9 mcg/mL. Blood levels with other infusion rates will vary in direct proportion to the infusion rate.

The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following I.V. or I.M. administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

CLINICAL TRIALS

Duodenal Ulcer

Cimetidine has been shown to be effective in the treatment of active duodenal ulcer and at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer. Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with *oral* cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates With Various Oral Cimetidine Dosage Regimens*				
REGIMEN	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
Week 4	68%	73%	80%	86%
Week 6	80%	80%	89%	–
Week 8	–	92%	94%	–

**Averages from controlled clinical trials.*

A U.S. double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with cimetidine 800 mg h.s., 79 to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer. Treatment with a reduced dose of cimetidine has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of one year's therapy with cimetidine 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of one year with cimetidine 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with cimetidine.

Active Benign Gastric Ulcer

Cimetidine has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with cimetidine 300 mg four times a day or with placebo for six weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size.

Endoscopically confirmed healing at six weeks was seen in significantly* more cimetidine-treated patients, than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

*p<0.05

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Cimetidine	Placebo
total at week 6	63/83 (76%)*	44/80 (55%)

*p=0.005

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with cimetidine than with placebo.

Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients:

A double-blind, placebo-controlled randomized study of continuous infusion cimetidine was performed in 131 critically ill patients (mean APACHE II score=15.99) to compare the incidence of upper gastrointestinal bleeding, manifested as hematemesis or bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage and/or which were accompanied by a drop in hematocrit of 5 percentage pints, or melena, with an endoscopically documented upper gastrointestinal source of bleed. 14% (9/65) of patients treated with cimetidine continuous infusion developed bleeding compared to 33% (22/66) of the placebo group. Coffee grounds was the manifestation of bleeding that accounted for the difference between groups. Another randomized, double-blind placebo-controlled study confirmed these results for an end point of upper gastrointestinal bleeding with a confirmed upper gastrointestinal source noted on endoscopy, and by post hoc analyses of bleeding episodes between groups.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Cimetidine significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis, and multiple endocrine adenomas. Use of cimetidine was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE

Cimetidine hydrochloride injection is indicated in:

1. Short-Term Treatment of Active Duodenal Ulcer. Most patients heal within 4 weeks, and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks (*see* **DOSAGE and ADMINISTRATION—Duodenal Ulcer**). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of *oral* cimetidine and antacids is not recommended since antacids have been reported to interfere with the absorption of oral cimetidine.

2. Maintenance Therapy for Duodenal Ulcer Patients at Reduced Dosage After Healing of Active Ulcer. Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to five years.

3. Short-Term Treatment of Active Benign Gastric Ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks.

4. Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients.

5. The Treatment of Pathological Hypersecretory Conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, and multiple endocrine adenomas).

CONTRAINDICATIONS

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

PRECAUTIONS

General: Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of cimetidine hydrochloride injection by intravenous bolus.

Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (*see* **ADVERSE REACTIONS**) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the conditions usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline, and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine, and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may

require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other dugs affected by the concomitant administration of cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378, and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups, and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine, as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology, or *in vitro* fertilizing capacity.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats, rabbits, and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

ADVERSE REACTIONS

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

The collection of this information has been derived largely from trials associated with oral cimetidine.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day, and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, and disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia, and A-V heart block have been reported with H_2-receptor antagonists.

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no casual relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and generalized exfoliative erythroderma have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia which may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions of up to 20 g have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24 hour period experienced mental deterioration with reversal on cimetidine discontinuation.

There have been two deaths in adults who have been reported to ingest over 40 g orally on a single occasion.

DOSAGE AND ADMINISTRATION

Parenteral Administration

In hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, cimetidine may be administered parenterally.

The doses and regimen for parenteral administration in patients with GERD have not been established.

Recommendations for Parenteral Administration

Intramuscular Injection: 300 mg q 6 to 8 hours (no dilution necessary). Transient pain at the site of injection has been reported.

Intravenous Injection: 300 mg q 6 to 8 hours. In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of a 300 mg dose, but should not exceed 2400 mg per day. Dilute cimetidine hydrochloride injection, 300 mg, in Sodium Chloride Injection (0.9%) or another compatible I.V. solution (*see* **Stability of Cimetidine Hydrochloride Injection**) to a total volume of 20 mL and inject over a period of not less than 5 minutes (*see* **PRECAUTIONS**).

Intermittent Intravenous Infusion: 300 mg q 6 to 8 hours, infused over 15 to 20 minutes. In some patients, it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of a 300 mg dose, but should not exceed 2400 mg per day.

Dilute cimetidine hydrochloride injection, 300 mg, in at least 50 mL of Dextrose Injection 5%, or another compatible I.V. solution (*see* **Stability of Cimetidine Hydrochloride Injection**).

Continuous Intravenous Infusion: 37.5 mg/hour (900 mg/day). For patients requiring a more rapid elevation of gastric pH, continuous infusion may be preceded by a 150 mg loading dose administered by I.V. infusion as described above. Dilute 900 mg cimetidine hydrochloride injection in a compatible I.V. fluid (*see* **Stability of Cimetidine Hydrochloride Injection**) for constant rate infusion over a 24-hour period. Note: Cimetidine may be diluted in 100 to 1000 mL; however, a volumetric pump is recommended if the volume for 24-hour infusion is less than 250 mL. In one study in patients with pathological hypersecretory states, the mean infused dose of cimetidine was 160 mg/hour with a range of 40 to 600 mg/hour.

These doses maintained the intragastric acid secretory rate at 10 mEq/hour or less. The infusion rate should be adjusted to individual patient requirements.

Stability of Cimetidine Hydrochloride Injection: When added to or diluted with most commonly used intravenous solutions, e.g., Sodium Chloride Injection (0.9%), Dextrose Injection (5% or 10%), Lactated Ringer's Injection, Sodium Bicarbonate Injection 5%, cimetidine hydrochloride injection should not be used after more than 48 hours of storage at room temperature.

NOTE: The products accompanying this insert are for I.M./I.V. use only. Much of the following relates to the use of oral cimetidine and is for informational purposes only. See Parenteral Administration (above) for specific dosing recommendations.

Duodenal Ulcer

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid

is the most important factor in duodenal ulcer healing (*see* **CLINICAL PHARMACOLOGY, Antisecretory Activity, Acid Secretion**). This is supported by recent clinical trials (*see* **CLINICAL PHARMACOLOGY, Clinical Trials, Active Duodenal Ulcer**). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime oral dosage regimen (h.s.).

In a U.S. oral dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions, (*see* **PRECAUTIONS—Drug Interactions**) and maximal patient convenience. Patients unhealed at four weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with cimetidine 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine oral regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (*see* **CLINICAL PHARMACOLOGY, Clinical Trials, Active Duodenal Ulcer**).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of *oral* cimetidine and antacids is not recommended since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg h.s., or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (*see* **CLINICAL PHARMACOLOGY, Clinical Trials**). 800 mg h.s. is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Prevention of Upper Gastrointestinal Bleeding

The recommended adult dosing regimen is continuous I.V. infusion of 50 mg/hour. Patients with creatinine clearance less than 30 cc/min. should receive half the recommended dose. Treatment beyond 7 days has not been studied.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Dosage Adjustment for Patients with Impaired Renal Function: Patients with severely impaired renal function have been treated with cimetidine. However, such usage has been very limited. On the basis of this experience the recommended dosage is 300 mg every 12 hours orally or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur, and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Patients with creatinine clearance less than 30 cc/min. who are being treated for prevention of upper gastrointestinal bleeding should receive half the recommended dose.

All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Cimetidine Hydrochloride Injection 150 mg base/mL, is supplied as follows:

NDC Number	Size
0703-**4602-04**	**2 mL**
0703-**4620-03**	**8 mL**

2 mL single dose vials packaged 25 per shelf pack.
8 mL multiple dose vials packaged 10 per shelf pack.

Store at controlled room temperature 15° to 30°C (59° to 86°F).
Do not refrigerate.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Revised: September 1997
Gensia Laboratories, Ltd.
Irvine CA 92618

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74252

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 74-252

3. NAME AND ADDRESS OF APPLICANT
Gensia Laboratories, Inc.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92618

4. LEGAL BASIS for ANDA SUBMISSION
The reference drug product is Tagamet by SmithKline Beecham Pharmaceuticals. This drug product has the same active ingredient, dosage form, strength, route of administration and conditions of use as Tagamet.

Two patents (3950333 and 4024271) exist for Tagamet which expired on 4/13/93 and 5/17/94, respectively. Market exclusivity for two indications and one route of administration (IV infusion) for Tagamet expired on 11/13/94, 3/7/94 and 11/13/92, respectively.

Firm certifies that it does not intend to market the drug product before 5/17/94 when both patents expire and that the drug product is not intended for the two indications and the IV infusion administration protected by the exclusivity as evidenced by their draft labeling.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Injection

9. AMENDMENTS AND OTHER DATES:

Firm:
- 7/30/92 - Original submission
- 9/02/92 - Three additional copies of the analytical methods.
- 5/26/95 - Amendment letter
- 7/10/96 - Amendment
- 3/28/97 - Amendment
- 9/10/97 - Amendment
- 11/06/97 - Telephone Amendment
- 11/24/97 - Fax Amendment

FDA:
- 8/14/92 - Acknowledgment letter
- 11/12/92 - Deficiency letter
- 12/6/95 - Deficiency letter
- 11/8/96 - Deficiency letter
- 09/02/97 - Fax deficiency

10. PHARMACOLOGICAL CATEGORY
Histamine H_2 receptor

11. Rx or OTC
Rx

antagonist

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection

14. POTENCY
300 mg base/2 mL; 2 mL and 8 mL vials

15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCl$
Mol. Wt.: 288.80

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
9/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74252

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #1
August 11, 1997

A. 1. ANDA: **74-252**

APPLICANT: Gensia Laboratories, LTD.
Attention: Ms. Elvia O. Gustavson
19 Hughes
Irvine, CA 92718

2. PRODUCT NAME: **Cimetidine Hydrochloride Injection**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 150 mg Base/mL, 2 and 8 mL fill volumes in 2 and 10 mL vials.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Antibiotics

B. 1. DATE OF INITIAL SUBMISSION: July 30, 1992
2. DATE OF AMENDMENT: March 28, 1997
3. RELATED DOCUMENTS: Microbiologists October 6, 1995 Review.
4. ASSIGNED FOR REVIEW: August 7, 1997

C. REMARKS: This application was submitted as a product and received a chemistry review of that process. Then it received a Microbiology overview and approval in 1995 (see above). This amendment is a gratuitous amendment for a sterilization process change.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided

8/11/97

James L. McVey

initialed by F. Fang or F. Holcombe

8/15/97

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74252

BIOEQUIVALENCE REVIEW(S)

NOV 23 1992

COPY FOR YOUR INFORMATION

Cimetidine HCl Injection, 300 mg/2 ml
Single Dose Vial(2 ml fill) & Multiple Dose Vial(8 ml fill)
ANDA # 74-252
Reviewer: Hoainhon Nguyen
WP #74252W.792

Gensia Pharmaceuticals
Irvine, CA
Submission Date:
July 30, 1992

Review of a Waiver Request

The firm has requested a waiver from in vivo bioavailability requirements for its Cimetidine HCl Injection, 300 mg/2 ml in single dose vial(2 ml fill) and multiple dose vial(2 ml fill), in accordance with 21 CFR 320.22 (c) (2).

Comments:

1. The test product is a parenteral drug solution intended for intramuscular and intravenous administration.

2. The formulation of the test product is identical to that of the currently approved Tagamet^{R} Injection, eq 300 mg base/2 ml, manufactured by SmithKline Beecham, as shown below:

Ingredients	SKB's Tagamet^{R} Formula(per ml)	Gensia's Formula(per ml)
Cimetidine HCL, USP equivalent to Cimetidine	150 mg	150 mg
Phenol, USP		
Sodium Hydroxide, NF		
Hydrochloric Acid		
Water for Injection, USP		

Although Hydrochloric Acid is not listed in the SKB's formula, its presence in the test product is judged to have no significant effect on the bioequivalence or safety and efficacy of the product. The Sodium Hydroxide/Hydrochloric Acid combination can be found in other parenteral drug products. Also, cimetidine is already present as the hydrochloride.

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Gensia Pharmaceuticals demonstrates that its Cimetidine HCl Injection, 300 mg/2 ml, in single dose and multiple dose vials, falls under 21 CFR 320.22 (c) (2) of the

Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in vivo bioavailability study be granted. The test product is deemed bioequivalent to the currently approved Tagamet[R] Injection, eq 300 mg base/2 ml, manufactured by SmithKline Beecham.

11/19/92

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED ATWU
FT INITIALED ATWU _____ Date: 11/22/92

HNguyen/11-17-92/ntp/111992/WP #74252W.792

cc: ANDA # 74-252 original, HFD-600(Hare), HFD-652(Wu, Nguyen), HFC-130(Allen), Drug File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74252

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 74-252

FIRM: Gensia Laboratories, Inc.
19 Hughes
Irvine, CA 92618

DOSAGE FORM: Injection STRENGTH: 300 mg (base)/2 mL

DRUG: Cimetidine Hydrochloride

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 8/19/97.

BIO STUDY INFORMATION: Waiver requested. Acceptable 11/22/92.

METHODS VALIDATION: Complete.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in both container sizes (2 mL and 10 mL).

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

The stability tests and specifications are as follows:

Description: Clear, colorless to slightly yellow solution

pH:

Assay: % label claim

impurities: %w/w

Sterility: passes

Bacterial endotoxins:

Particulate matter:

LABELING: Satisfactory. See review dated 10/22/97.

STERILIZATION VALIDATION: Acceptable 8/11/97.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

The firm initially manufactured two stability lots XP2C015 and XP2C018 . Two additional stability batches (XP6C016 and XP6C016F1 , were manufactured to validate the Federgari Sterilization process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The proposed production batch size is

RECOMMENDATION: Approvable.

SIGNATURE: DATE: 11/13/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74252

CORRESPONDENCE

ANDA 74-252

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

NOV 8 1996

Dear Mr. Harrigan:

This is in reference to your abbreviated new drug application dated July 30, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL.

Reference is made to your amendment dated July 10, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

INSERT:

CLINICAL PHARMACOLOGY

Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients:

> ... source of bleed. 14% (9/65) of patients treated with cimetidine continuous infusion developed bleeding compared to 33% (22/66) of the placebo group. Coffee grounds was the manifestation of bleeding that accounted for the difference between groups. Another randomized, double-blind ...

Please revise your insert labeling, as instructed above, and submit final print. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

We note that this letter represents the second occasion on which significant (MAJOR) chemistry, manufacturing, and/or controls deficiencies have been identified which have precluded approval of your application. In an effort to facilitate resolution of these deficiencies, we encourage you to contact Kassandra Sherrod, Project Manager, at (301) 594-1300, for further clarification or assistance in providing a satisfactory response to each of the deficiencies.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies and comments provided. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed.

The response to this letter will be considered a MAJOR AMENDMENT and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

11/8/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

GENSIA
LABORATORIES, LTD.

May 26, 1995

AMENDMENT

N/AC DRAFT

Mr. Doug Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-252
Cimetidine Hydrochloride Injection
150 mg Base/mL

MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our ANDA submitted on July 30, 1992, providing for Cimetidine Hydrochloride Injection, 150 mg Base/mL.

In accordance with the provisions of Section 314.60 of the Code of Federal Regulations, Title 21, we hereby amend our application to provide the additional information requested in your letter dated November 12, 1992.

Attached please find copies of all requested information and documentation for your review and approval.

We trust you will find the information in this amendment satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (714) 455-4724.

Sincerely,

Donald J. Harrigan / Ellen O. Gus[illegible]

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs/Compliance

5-31-95

RECEIVED
MAY 30 1995
GENERIC DRUGS

s:\cim74252\defresp1

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Bracknell Beeches, Old Bracknell Lane, Bracknell, Berkshire RG12 7BW
44-344-308803 ■ FAX 44-344-360515

GENSIA
LABORATORIES, LTD.

ORIG AMENDMENT
AC

RECEIVED

JUL 11 1996

GENERIC DRUGS

July 10, 1996

Ms. Kassandra Sherrod
Office of Generic Drugs
Center for Drugs Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 254-E
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-252
Cimetidine Hydrochloride
Injection
150 mg Base/mL

Dear Ms. Sherrod:

Pursuant to our telephone conversation of July 10, 1996, we are providing you with two desk copies of the deficiency response for Cimetidine Hydrochloride Injection, 150 mg Base/mL, dated February 16, 1996.

Please be advised that a copy of the deficiency response was simultaneously provided to the FDA Los Angeles District Office. We are currently obtaining verification that they also received this document.

As requested, three photo copies of the Federal Express airway bill number associated with our submission to the Agency are not being provided today. They will be provided as soon as the Federal Express Company can verify receipt and delivery. Our initial contact with the Federal Express Company indicated that it will take two weeks to retrieve the data we requested.

We would appreciate an expeditious review of the deficiency response for Cimetidine Hydrochloride Injection.

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Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Bracknell Beeches, Old Bracknell Lane, Bracknell, Berkshire RG127BW
44-344-308803 ■ FAX 44-344-360515

Should you have any questions or require further clarification, please do not hesitate to contact Elvia Gustavson, Associate Director Regulatory Affairs at (714) 455-4724.

Sincerely,

Elvia Gustavson
Associate Director, Regulatory Affairs

s:\cim74752\71096.ltr

GENSIA
LABORATORIES, LTD.

March 28, 1997

NDA ORIG AMENDMENT
N/AC FPL

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-252
Cimetidine Hydrochloride Injection
150 mg Base/mL

RECEIVED
MAR 3 1 1997
GENERIC DRUGS

MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our ANDA submitted on July 30, 1992, providing for Cimetidine Hydrochloride Injection, 150 mg Base/mL. Reference is also made to our amendment dated July 10, 1996. Further reference is made to the Agency's deficiency letter dated November 8, 1996.

In accordance with the provisions of Section 314.60 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information as requested.

At this time, we wish to amend this application to accomplish the terminal sterilization of Cimetidine Hydrochloride Injection in the The sterilization validation summary for Cimetidine Hydrochloride Injection, is provided in **Attachment 8.** The purpose of this report is to establish, verify and document that cimetidine hydrochloride Injection qualifies for the

The has been demonstrated to provide better control over the uring the cool down period; thereby decreasing the maximum accumulated o the product. Therefore, the provides the in the original application. As a result, the drug product as found to have a lower level of

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Brackneil Beecnes, Old Brackneil Lane, Brackneil, Berkshire RG127BW
44-344-308803 ■ FAX 44-344-360515

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Two additional lots, one of each fill size, were manufactured as stability batches. Each lot was sublotted relative to the used. The sublots were in either the was utilized for the of the developmental stability lots as presented in the original application. The was used to support the future use of this All other manufacturing, chemistry and control procedures are in accordance with the procedures submitted in the original application. The executed batch records supporting this amendment are provided in **Attachment 9**.

In addition to the requested revisions to the Finished Product and Stability specifications, we have eliminated As discussed in the Stability Report, the results of this test were found not to be stability-indicating for the drug product.

We trust you will find the information in this amendment satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (714) 455-4709 or Ms. Elvia O. Gustavson, Associate Director, Regulatory Affairs, at (714) 455-4724, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

cc: Ms. Elaine Messa
Food and Drug Administration
Los Angeles District Office
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

SEP 2 1997

Chemistry Comments to be Provided to the Applicant

ANDA: 74-252 APPLICANT: Gensia Laboratories, LTD.

DRUG PRODUCT: Cimetidine Hydrochloride Injection,
300 mg/2 mL

The deficiencies presented below represent FACSIMILE deficiencies.

Deficiencies:

1. It was stated that the response factor for was based on a single experiment since not enough reference material was available. Given that this is the in addition to the fact that the final limits for individual and total degradants are linked to the determination of this degradant, its response factor should be accurately determined.

   Alternatively, if you are unable to obtain enough reference material, you may assign it the same response factor as

   Stability data reports along with release and stability limits should be revised accordingly.

2. We acknowledge the revision in the limits for individual and total impurities. It was noted that the finished product and stability limits were identical. Typically, the release limits are more stringent than shelf-life limits. Based on data obtained from samples it would appear that the release limits could be reduced.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

GENSIA®
LABORATORIES, LTD.

September 10, 1997

FAL

NEW CORRESP

NC

NAF
11/5/97

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-252
Cimetidine Hydrochloride Injection
150 mg Base/mL

FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to our ANDA submitted on July 30, 1992, providing for Cimetidine Hydrochloride Injection, 150 mg base/mL. Further reference is made to the Agency's letter dated September 2, 1997.

In accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information as requested.

We trust you will find the information in this amendment satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (714) 455-4709 or Ms. Elvia O. Gustavson, Associate Director, Regulatory Affairs, at (714) 455-4724, or by facsimile at (714) 583-7351.

Sincerely,

Elvia O. Gustavson

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

RECEIVED
SEP 11 1997
GENERIC DRUGS

cc: Ms. Elaine Messa
Food and Drug Administration
Los Angeles District Office
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
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44-344-308803 ■ FAX 44-344-360515

Gensia Laboratories, Ltd.
Cimetidine Hydrochloride Injection
ANDA 74-252
Response to Deficiency Letter dated September 2, 1997

A. *Chemistry Deficiencies:*

1. *It was stated that the response factor for as based on a single experiment since not enough reference material was available. Given that this is the n addition to the fact that the final limits for individual and total degradants are linked to the determination of this degradant, its response factor should be accurately determined.*

Alternatively, if you are unable to obtain enough reference material, you may assign it the same response factor as cimetidine amide (the compound from which it is derived). Stability data reports along with release and stability limits should be revised accordingly.

Gensia has not been able to obtain eference material of known purity. Therefore we elected to assign ne same response factor as The stability data were recalculated accordingly. Additionally, the release and stability limits for and Total impurities were tightened based on the recalculated stability results. The table below lists the stability specifications for the following .

Impurity	Previous Shelf Specification	Current Shelf Specification

"

The updated stability report and Finished Product Test Specifications and Data Sheet are provided in **Attachments 1** and **2**, respectively.

Gensia Laboratories, Ltd.
Cimetidine Hydrochloride Injection
ANDA 74-252
Response to Deficiency Letter dated September 2, 1997

A. *Chemistry Deficiencies:*

2. *We acknowledge the revision in the limits for individual and total impurities. It was noted that the finished product and stability limits were identical. Typically, the release limits are more stringent that shelf-life limits. Based on data obtained from samples it would appear that the release limits could be reduced.*

The release limits for impurities have been reduced as listed below:

Impurity	Previous Release Specification	Current Release Specification

The revised Finished Product Testing Specifications and Data Sheet is provided in **Attachment 2.**

B. *Labeling Deficiencies:*

INSERT

1. *DESCRIPTION*

Include the routes of administration in this section.

2. *CLINICAL PHARMACOLOGY*

a. *Use the abbreviation "p.o." rather than "po" in the second table.*

b. *Make the following revision in the first sentence following the second table, "... hydrogen ion...", (spelling "ion").*

c. *Delete the first sentence in the subsection, "Pharmacokinetics".*

d. *Clinical Trials*

Make consistent use of subsection and sub-subsection headings throughout this subsection. For example:

i. *"Duodenal Ulcer" is a subsection heading of this subsection and should be differentiated in format.*

ii. *"Maintenance Therapy in Duodenal Ulcer" is a subsection heading of the subsection "Duodenal Ulcer" and should appear with the same format as the other subsection, "Active Duodenal Ulcer".*

3. *INDICATIONS AND USAGE*

Revise the fourth indication to have format (case) consistent with the other indications listed.

4. *PRECAUTIONS*

Drug Interactions (Third paragraph)

In the first sentence, "...extended-release...", (hyphen).

5. *OVERDOSAGE*

Add the following as the second sentence to the second paragraph:

The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

6. *DOSAGE AND ADMINISTRATION*

a. *Add the following text as the second paragraph of the Parenteral Administration subsection:*

The doses and regimen for parenteral administration in patients with GERD have not been established.

b. *Recommendations for Parenteral Administration*

i. *Revise the subsection headings in this subsection to appear with the same prominence.*

ii. *Make the following revision in the fourth paragraph, "...Dextrose Injection 5%, ...".*

c. *Stability of Cimetidine Hydrochloride Injection*

Make the following revision, "...Sodium Bicarbonate Injection 5%,...".

d. *Duodenal Ulcer*

i. *Active Duodenal Ulcer*

A. *First sentence, "...PHARMACOLOGY, Antisecretory Activity, Acid...".*

B. *Second sentence, "...see CLINICAL PHARMACOLOGY, Clinical...".*

ii. *Fifth Paragraph*

...see CLINICAL PHARMACOLOGY, Clinical...

e. *Active Benign Gastric Ulcer*

...see CLINICAL PHARMACOLOGY, Clinical...

7. *HOW SUPPLIED (First line)*

Indicate that the strength of your product is in terms of the base.

Please revise your package insert labeling, as instructed above, and submit final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A side-by-side comparison of the revised labeling to the labeling presented in our last submission including annotated differences and an explanation of each revision is provided in **Attachment 3**. Additionally, twelve (12) samples of the final printed package insert are provided in **Attachment 4.**

GENSIA
LABORATORIES, LTD.

November 6, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Cimetidine Hydrochloride Injection
ANDA 74-252

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application (ANDA) for Cimetidine Hydrochloride Injection, submitted on July 30, 1992. Further reference is made to the telephone conversation of November 6, 1997 between Ms. Kassandra Sherrod and Ms. Rosalie A. Lowe, Gensia Laboratories, Ltd.

In accordance with the provisions of Section 314.96 of the Code of Federal Regulations, Title 21, we hereby amend our application to provide the additional information as requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate to contact Ms. Elvia Gustavson, Associate Director, Regulatory Affairs, at (714) 455-4724, myself at (714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

S:\CIM74252\DEFRESP\AMEND6.WPD

RECEIVED
NOV 7 1997
GENERIC DRUGS

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
Department of Health and Human Services
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Bracknell Beecnes, Old Bracknell Lane, Bracknell, Berkshire RG127BW
44-344-308803 ■ FAX 44-344-360515

GENSIA
LABORATORIES, LTD.

gulatory Affairs
csimile Transmittal

Please note:

This is page 1 of 13 pages. If you do not receive the entire transmittal, please notify our office at your earliest convenience.

ORIG AMENDMENT

N/FA

e: November 24, 1997

Mr. Andrew Langowski
Office of Generic Drugs, FDA

FAX number: 301-443-3839

m: Mr. Donald J. Harrigan
FAX 714-583-7351

ANDA 74-252; Cimetidine Hydrochloride Injection

---

ar Mr. Langowski:

ase find attached the telephone amendment for Cimetidine Hydrochloride Injection.

ou should have any questions, please do not hesitate to contact me at (714) 455-4709.

74252\DEFRESP\112497.FAX

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia, Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Europe Ltd. ■ Genaresa House, Bracknell Beeches, Berkshire RG12 7BW, England ■ Tel: 44-344-308803 ■ FAX: 44-344-360515

NOV-24-97 MON 05:59 PM GENSIA REG AFFAIRS FAX NO. 714 583 7351 P.
714 583 7351

FACSIMILE AMENDMENT

SEP 2 1997

ANDA/~~AADA~~: 74-252

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 ([redacted])

TO: APPLICANT Gensia Laboratories PHONE (714) 455-4709
ATTN: Donald J. Harrigan, R.Ph. FAX 714-583-7351

FROM: Kassandra Sherrod, PROJECT MANAGER (301-~~594-1300~~ 827-5849)

Dear Sir/~~Madam~~:

This facsimile is in reference to your abbreviated new drug/~~antibiotic~~ application dated July 30, 1992, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Cimetidine Hydrochloride Injection, 150mg Base/mL

Reference is also made to your amendment(~~s~~) dated March 28, 1997.

Attached are 4 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
X:\new\ogdadmin\faxtrak\faxcov.fax

GENSIA®
LABORATORIES, LTD.

ember 24, 1997

Douglas Sporn
ce of Generic Drugs
nter for Drug Evaluation and Research
od and Drug Administration
tro Park North II, HFD-600
ention: Documentation and Control Room, Room 150
00 Standish Place
ckville, MD 20855-2773

RE: Cimetidine Hydrochloride Injection
ANDA 74-252

TELEPHONE AMENDMENT

ear Mr. Sporn:

eference is made to our abbreviated new drug application (ANDA) for Cimetidine Hydrochloride jection, submitted on July 30, 1992. Further reference is made to the telephone conversation November 24, 1997 between Mr. Andrew Langowski and Mr. Donald Harrigan, Gensia aboratories, Ltd.

n accordance with the provisions of Section 314.96 of the Code of Federal Regulations, Title 21, e hereby amend our application to provide the additional information as requested. Specifically, e are providing a revised commercial stability protocol. Included in the protocol is our ommitment to test vials stored in the upright and inverted positions on the first three lots of each roduct size. If no differences are noted, Gensia will discontinue testing of upright samples and ubmit in the annual report a revised commercial stability protocol reflecting the testing of the nverted samples only.

We trust you will find the information in this amendment satisfactory for your review and pproval. If there are any questions concerning this application, please do not hesitate to ontact Ms. Elvia Gustavson, Associate Director, Regulatory Affairs, at (714) 455-4724, myself at 714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Elvia O. Gustavson

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
Department of Health and Human Services
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

S:\CIM74252\DEFRESP\AMEND7.WPD

NOV-24-97 MON 06:01 PM GENSIA REG AFFAIRS FAX NO. 714 583 7351 P.01

GENSIA
LABORATORIES, LTD.

September 2, 1992

Dr. Roger Williams
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room
Room 150
7500 Standish Place
Rockville, MD 20855

mail 9-8-92
NEW CORRESP

RE: ANDA 74-252
Cimetidine Hydrochloride
Injection, 300 mg Base/2mL

Dear Dr. Williams:

Reference is made to our Abbreviated New Drug Application, Cimetidine Hydrochloride Injection submitted July 30,1992.

In accordance with the provisions of section 314.70(c) of the Code of Federal Regulations, Title 21, we hereby amend our application.

Per your letter dated August 14, 1992 we are submitting **three additional copies** of the analytical methods and descriptive information needed to perform the tests on the samples and validate the analytical methods.

If there are any questions regarding this matter, please contact the undersigned at (714) 455-4709.

Sincerely,

Donald J. Harrigan /dmk

Donald J. Harrigan, R.Ph.
Regulatory Affairs Manager

RECEIVED
SEP 4 1992
GENERIC DRUGS

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Pharmaceuticals, Inc. ■ 11025 Roselle Street, San Diego, CA 92121-1204 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe Ltd. ■ Wolfelands, Westerham, Kent, TN16 1RQ ■ 959-63093 ■ FAX 959-64500

ANDA 74-252

NOV 12 1992

Gensia Laboratories, Inc.
Attention: Mr. Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

Dear Mr. Harrigan:

This is in reference to your abbreviated new drug application dated July 30, 1992, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Injection, Eq 300 mg Base/2 mL.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

Container:

1. The strength of this preparation should be prominent and stated as:

   300 mg/2 mL*
   (150 mg/mL)

   Note: The "300 mg/2 mL" should be the more prominent expression of strength. In addition, the asterisk is not needed for the 2 mL vial.

2. Revise the "each 2 mL" statement to read:

   * Each mL contains: Cimetidine hydrochloride equivalent to 150 mg cimetidine; phenol 5 mg. . .

3. Revise to read and include this on the main panel:

   FOR IM or IV USE
   DILUTE BEFORE IV USE

Carton:

1. You have not included the quantity of vials in each carton.

2. See comments under Container.

Insert: Revise your insert labeling to be in accord with the enclosed labeling guidance (Cimetidine Hydrochloride Injection; Revised June 1992).

Please revise your labels and labeling, then prepare and submit a draft copy for our review.

In addition to responding to these deficiencies, please note that is deficient and that the holder has been notified of the deficiencies.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

for/ 11/10/92

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Labeling Guidance

Imp to Bio 505(j)(2)(A) ... 8/7/92 Tulin ... ok 8/11/92

GENSIA
LABORATORIES, LTD.

July 30, 1992

RECEIVED
AUG 5 1992
GENERIC DRUGS

Dr. Roger Williams
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room
Room 150
7500 Standish Place
Rockville, MD 20855

RE: Cimetidine Hydrochloride Injection

Dear Dr. Williams:

In accordance with Section 314.55 of the Code of Federal Regulations, Title 21 we hereby submit an Abbreviated New Drug Application for Cimetidine Hydrochloride, Injection, a liquid parenteral preparation supplied as 300 mg per 2 mL. The drug is packaged in a single dose vial (2 mL fill) and a multiple dose vial (8 mL fill).

Cimetidine Hydrochloride Injection, is indicated for short-term treatment of duodenal ulcer; maintenance therapy for duodenal ulcer patients; short-term treatment of active benign gastric ulcer and pathological hypersecretory conditions.

Cimetidine Hydrochloride Injection, 300 mg per 2mL (2 mL and 8 mL fill) is the generic version of SmithKline Beecham Pharmaceuticals Tagamet® (Cimetidine Hydrochloride Injection). SmithKline Beecham's product appears in the FDA listing entitled "Approved Drug Products with Therapeutic Equivalence Evaluation". A comparison of the products is provided in Section IV of this application.

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Pharmaceuticals, Inc. ■ 11025 Roselle Street, San Diego, CA 92121-1204 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe Ltd. ■ Wolfelands, Westerham, Kent, TN16 1RQ ■ 959-63093 ■ FAX 959-64500

The propsed product will be bottled in USP Type I, 2 mL and 10 mL glass vials. The vials will be sealed with stoppers from the

The application consists of two volumes and has been formatted in accordance with Policy and Procedure Guide # 30-91 issued April 10, 1991.

Two Research & Development lots were manufactured on production equipment and in a validated The of that can be found in Section XI (Manufacturing and Processing) Item 1.

Three copies of the methods validation package have been included in the archival copy in a separate envelope marked "Methods Validation Data". Also, four copies of the proposed labeling have been provided in a separate envelope marked "Labeling" in the archival copy of the application.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please contact the undersigned at (714) 455-4731.

Sincerely,

Donald J. Harrigan

Donald J.Harrigan, R.Ph.
Regulatory Manager Affairs

DH:mew
cimetidinewp

ANDA 74-252

Gensia Laboratories, Inc.
Attention: Donald J. Harrigan
19 Hughes
Irvine, CA 92718-1902

AUG 14 1992

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG: Cimetidine Hydrochloride Injection, Eq 300 mg Base/2 mL

DATE OF APPLICATION: July 30, 1992

DATE OF RECEIPT: August 3, 1992

We will correspond with you further after we have had the opportunity to review the application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

/R
Roger L. Williams, M.D. 8-14-92
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-252
DUP/Division File
HFC-130/JAllen
HFD-636/BArnwine/ 8/13/92
HFD-630/RPollock/WTurner
HFD-600/Reading File
R/D initialed by GJohnston
74252ack.ltr(acknow)jkg/8-11-92
F/T by jkg/8-12-92
Acknowledgement Letter!
8/13/92

ANDA 74-252

Gensia Laboratories, Ltd.
Attention: Mr. Donald J. Harrigan, R.Ph.
19 Hughs
Irvine, CA 92718-1902

DEC 6 1995

Dear Mr. Harrigan:

This is in reference to your abbreviated new drug application dated July 30, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL.

Reference is made to your amendment dated May 26, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

CONTAINER: 2mL and 8mL

1. Place "150 mg/mL" in parenthesis and include "of cimetidine" so one knows that the strength is not expressed as the hydrochloride

2. Revise the net quantity statement on the 2 mL label to read:

   2 mL Vial

CARTON: 25 x 2mL and 10 x 8 mL

1. You have indicated in the HOW SUPPLIED section of your package insert that the 8 mL vials will be packaged 10 per shelf pack. However, you have not submitted any labeling for this shelf pack. Please prepare and submit the carton labeling for this container size.

2. See comments under CONTAINER.

3. Indicate the quantity of vials contained in each shelf pack.

INSERT:

1. DESCRIPTION

   a. Revise the first paragraph, last sentence, to read:

      The structural formula of cimetidine hydrochloride is...

b. Paragraph 2, line 2 - Cimetidine has a bitter...

c. Add "HCl" to the structural formula.

2. CLINICAL PHARMACOLOGY

a. Chemically Stimulated

i. Table - Delete the hyphen between "2" and "1/2" in the last column.

ii. Last paragraph, line 2 - Ensure the "number" and "unit of expression of strength" appear on the same line. Revise throughout the remainder of the text of the insert. [e.g., 37.5 mg/hour]

b. "Clinical Trials" is a subsection under CLINICAL PHARMACOLOGY and should not have the same prominence as the section heading. Please revise.

c. Insert the following text to appear as the penultimate subsection:

Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients:

A double-blind, placebo-controlled randomized study of continuous infusion cimetidine was performed in 131 critically ill patients (mean APACHE II score=15.99) to compare the incidence of upper gastrointestinal bleeding, manifested as hematemesis or bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage and/or which were accompanied by a drop in hematocrit of 5 percentage pints, or melena, with an endoscopically documented upper gastrointestinal source of bleed. 14% (9/65) of patients treated with cimetidine continuous infusion developed bleeding that accounted for the difference between groups. Another randomized, double-blind placebo-controlled study confirmed these results for an end point of upper gastrointestinal bleeding with a confirmed upper gastrointestinal source noted on endoscopy, and by post hoc analyses of bleeding episodes between groups.

3. INDICATIONS AND USAGE

Insert the following text as the fourth indication: ("The Treatment of Pathological Hypersecretory..." will become the fifth indication.)

Prevention of upper gastrointestinal bleeding in critically ill patients.

4. PRECAUTIONS

a. Drug Interactions - Insert the following text to appear as the penultimate paragraph:

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

b. Pediatric Use - Replace "children" with "pediatric patients". [2 Places]

c. Insert the following text to appear as the last subsection:

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

5. ADVERSE REACTIONS

a. Hepatobiliary - Insert the following text as the last sentence of the first paragraph:

However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

b. Insert the following text to appear as the last subsection:

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

6. OVERDOSAGE

Insert the following text to appear as the last sentence of the third paragraph:

An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24 hour period experienced mental deterioration with reversal on cimetidine discontinuation.

7. DOSAGE AND ADMINISTRATION

a. Stability of Cimetidine Hydrochloride Injection, lime 3 - ...5% Sodium Bicarbonate Injection, cimetidine hydrochloride injection should not...

b. Add the following text to appear as the subsection after "Active Benign Gastric Ulcer":

Prevention of Upper Gastrointestinal Bleeding

The recommended adult dosing regimen is continuous I.V. infusion of 50 mg/hour. Patients with creatinine clearance less than 30 cc/min. should receive half the recommended dose. Treatment beyond 7 days has not been studied.

c. Dosage Adjustment for Patients with Impaired Renal Function

i. Line 3 - ...300 mg every 12...

ii. Add the following text to appear as the penultimate paragraph:

Patients with creatinine clearance less than 30 cc/min. who are being treated for prevention of upper gastrointestinal bleeding should receive half the recommended dose.

Please revise your container labels, carton and insert labeling, then prepare and submit final printed container labels, carton labeling and draft package insert labeling.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

12/5/95

Frank O. Holcombe, Ur., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research